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(54) Title: USE OF 4-(4-CHLOROPHENYL-SULPHONYLCARBAMOYL) BENZOYL-L-VALYL-L-PROLINE 1(*RS*)-(1-TRIFLUOROACETYL-2-METHYLPROPYL) AMIDE IN THE TREATMENT OF VASCULAR DISEASES

(57) Abstract

The use of the elastase inhibitor 4-(4-chlorophenyl-sylphonylcarbamoyl)benzoyl-L-valyl-L-proline 1(*RS*)-(1-trifluoroacetyl-2-methylpropyl) amide, or a pharmaceutically acceptable salt thereof, in the treatment of certain vascular diseases in which neutrophils are involved, e.g. cardiovascular disease such as myocardial ischaemia, cerebrovascular disease such as stroke, peripheral vascular disease such as intermittent claudication, as well as in impaired reperfusion states such those associated with reconstructive vascular surgery.

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USE OF 4-(4-CHLOROPHENYL-SULPHONYLCARBAMOYL) BENZOYL-L-VALVYL-L-PROLINE 1(RS)-1(1-TRIFLUOROACETYL-2-METHYLPROPYL) AMIDE IN THE TREATMENT OF VASCULAR DISEASES

Technical Field

The present invention concerns a new pharmaceutical agent for use in the treatment of certain vascular diseases and related conditions in which neutrophil participation is involved or implicated. More particularly, the invention concerns the use of the known compound 4-(4-chlorophenylsulphonylcarbamoyl)benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide, or a pharmaceutically acceptable salt thereof, in the therapy or prophylaxis of certain vascular diseases and related conditions in which neutrophils are involved or implicated. Such diseases and related conditions include (but are not limited to), for example, myocardial ischaemia and related conditions associated with coronary artery disease such as angina and infarction, cerebrovascular ischaemia such as transient ischaemic attack and stroke, peripheral occlusive vascular disease such as intermittent claudication and critical limb ischaemia, venous insufficiency such as venous hypertension, varicose veins and venous ulceration, as well as impaired reperfusion states such as those associated with reconstructive vascular surgery, thrombolysis and angioplasty.

Background to Invention

The most frequent precipitating cause of acute myocardial ischaemia (unstable angina and myocardial infarction) is a thrombus occluding an atherosclerotic coronary artery. Early intravenous or intracoronary administration of thrombolytic agents, such as streptokinase or tissue plasminogen activator (t-PA), can reopen the occluded artery in approximately 75% to 85% of patients. However, a major problem associated with thrombolytic therapy is rethrombosis (and subsequent reocclusion) of the successfully recanalized artery, the rate of which has been reported to be as high as 30%. Failure to maintain coronary blood flow may result from continued *in vivo* platelet and neutrophil aggregation, the release of arachidonic acid metabolites which cause coronary spasm, or from capillary plugging by microemboli. In addition, there is evidence that reperfusion itself

can lead to myocardial damage and detrimental effects on myocardial function mediated via reperfusion arrhythmias, depressed myocardial contractility and modulation of coronary vasomotor tone. At least part of these detrimental effects of reperfusion is related to activation of, and plugging by, neutrophils of the arterioles and capillaries that takes place during and following ischaemia. Reperfusion itself is often impaired ('no reflow' phenomenon) which itself contributes to tissue injury and thus recovery from ischaemia. The process of neutrophil trapping, activation, tissue damage and further activation and trapping of neutrophils, is believed to contribute to the progression of the underlying disease condition such as myocardial damage. Further, the loss of, or impairment to, the endothelium during neutrophil infiltration of tissues may also result in loss endothelium-derived relaxing factors. These latter phenomena may also potentiate rethrombosis and loss of coronary vascular reserve.

Nevertheless, the ingress into, and activation of, neutrophils in tissues following periods of ischaemia is believed to be involved in the natural scarring and healing processes and so, for adequate therapeutic or prophylactic benefit, a pharmaceutical agent needs to demonstrate the required balance of effects. There is thus a continuing clinical need to find a means to ameliorate injury in damaged or compromised vascular tissues such as reperfused tissues and thus effect a sustained treatment for vascular diseases and related conditions such as any one of those mentioned above. It has now been found that the therapeutic agent referred to above is useful in such treatment and this is a basis for the present invention.

In addition, other cardiovascular conditions in which the above agent may be useful for therapy or prophylaxis include shock (septic and circulatory), trauma, oedema, burns (including respiratory consequences), acute organ transplant failure and renal injury/failure.

Disclosure of Invention

According to the present invention there is provided a novel therapeutic agent for use in the therapeutic or prophylactic treatment

of a vascular disease or related condition in which neutrophils are involved or implicated (such as any one of those mentioned above) in a mammal, especially a human, in need thereof which agent comprises 4-(4-chlorophenylsulphonylcarbamoyl)benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide, or a pharmaceutically acceptable salt thereof (hereinafter referred to as "the Agent").

It should be noted that, although the active chemical entity is named here as "1(RS)" isomeric mixture, the invention also includes the use of a mixture containing any ratio of the "1(R)" and "1(S)" isomers of the above named entity, or the pharmaceutically acceptable salts thereof.

As another aspect of the invention, there is provided a method of therapeutic or prophylactic treatment of a vascular disease or related condition in which neutrophils are involved or implicated (such as any one of those mentioned above) in a mammal, especially a human, with the Agent.

As a further aspect of the invention, there is provided the use of the Agent in the manufacture of a medicament for the therapeutic or prophylactic treatment of a vascular disease or related condition in which neutrophils are involved or implicated (such as any one of those mentioned above).

The Agent is particularly suitable, for example, in the therapeutic or prophylactic treatment of coronary artery disease and related conditions (and especially of myocardial ischaemia or angina).

The active entity of the Agent, 4-(4-chlorophenylsulphonyl-carbamoyl)benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide, and its production are described in US patent 4,910,190 where it was referred to as 3(RS)-[4-[(4-chlorophenyl)-sulfonylamino-carbonyl]phenylcarbonyl]-L-valyl-N-[3-(1,1,1-trifluoro-4-methyl-2-oxopentyl)]-L-prolinamide, but the name given hereinabove is now preferred. It is noted that Dess-Martin periodinane, described as the preferred oxidant and used in the final step for the production of the compound in Examples 104 and 121 of said US patent, may in certain circumstances constitute an explosive hazard. Accordingly, it may be preferred to use an alternative oxidant for preparing the ketone from the corresponding alcohol.

Alternative methods which may be useful include the use of oxalyl chloride, dimethyl sulfoxide and a tertiary amine (with the best results being obtained with 10-20 equivalents of oxidising agent); the use of acetic anhydride and dimethyl sulfoxide; the use of chromium trioxide pyridine complex in methylene chloride; and the use of alkaline potassium permanganate solution. For example, the compound may be obtained from the corresponding alcohol in approximately 60% yield using two equivalents of the latter oxidant. The compound may be formulated in conventional manner, for example, as described in the accompanying Example and then subsequently diluted to the required concentration with physiological saline just prior to its use.

As a yet further aspect of the invention, there is provided a method of treatment of a vascular disease or related condition in which neutrophils are involved or implicated, in a mammal, especially a human, in need thereof which comprises administering the Agent in combination with one or more other agents indicated for use in treating said disease or related condition. Such agents include those indicated to affect the rate or magnitude of reperfusion or to prevent reocclusion or, in the case of coronary artery disease, to prevent cardiac arrhythmia, fibrillation and/or myocardial damage. Such an agent may typically be, for example, a thrombolytic agent, an anticoagulant, an antithrombotic substance, a vasodilator, an antiarrhythmic or antifibrillatory agent, a thromboxane antagonist, an oxygen free-radical scavenger, or an inhibitor of transglutaminase activity, especially of Factor XIIIa activity.

Suitable thrombolytic agents include, for example, those of the type known as plasminogen activators, for example streptokinase, urokinase, prourokinase and tissue plasminogen activator (t-PA), or their derivatives, analogues or conjugates, or a mixture thereof, obtained from natural sources or by recombinant genetic engineering methodology. One particular thrombolytic agent of particular interest is t-PA.

Suitable anticoagulants include, for example, heparin, warfarin, aspirin, anisindione, phenidone and bishydroxycoumarin. Suitable antithrombic substance includes any substance which prevents or impedes the development of blood clots, including, for example,

human activated protein C or an analogue thereof, as well as, for example, hirudin or an analogue or derivative, for example as noted in U.S. patent 4,944,943. Suitable vasodilators include, for example, a nitrate, papaverine, nicotinic acid and cyclandelate. Suitable antiarrhythmic or antifibrillatory agents include, for example, quinidine, procainamide, disopyramide, lidocaine, tocainide, phenyltoin, flecainide, encainide, amiodarone, bretylium, doflilium, verapamil, diltiazem, sotalol, propranolol, nadolol, metoprolol and 4-(N-ethyl-N-phenylamino)-1,2-dimethyl-6-(methylamino)pyrimidinium chloride.

Suitable oxygen free radical scavengers include, for example, superoxide dismutase, for example the copper/zinc form of cow or human origin, and mercapto-containing inhibitor of angiotensin converting enzyme (ACE), such as, for example, captopril, zofenopril, fentiapril or fosinopril. Suitable thromboxane antagonists include, for example, (4Z)-6-[[2RS,4RS,5SR]-2-(2-chlorophenyl)-4-(2-hydroxyphenyl)-1,3-dioxan-5-yl)]hex-4-enoic acid.

In such a method of the invention, the individual therapeutically active agents may be administered simultaneously, sequentially or separately, by the route and in the dosage which is well known in the art and which is customary for the particular active agents involved.

In use, the Agent will generally be administered for prophylactic or therapeutic treatment in the form of a conventional pharmaceutical composition, for example, as generally described in US patent 4,910,190, and preferably as a sterile intravenous injection. The formulations may be made by conventional procedures well know in the art. An illustrative formulation providing a solution containing a concentration of 10 mg/mL of the Agent and suitable for use as an injectable solution is described in the accompanying Example.

In general, the Agent will be administered to humans so that a daily dose in the general range, for example, 0.5 to 20 mg/kg (especially 3 to 7 mg/kg) of 4-(4-chlorophenylsulphonyl-carbamoyl)-benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)-amide, or an equivalent amount of a pharmaceutically acceptable salt thereof, is received given intravenously. However, it will be readily

understood that it may be necessary to vary the dose of therapeutic product administered in accordance with well known medical practice to take account of the nature and severity of the disease or condition under treatment, any concurrent therapy, and of the age, weight and sex of the patient receiving treatment. In addition, it will be appreciated that in acute situations the Agent may be administered initially as a first bolus dose followed by smaller doses at regular intervals or by means of a continuous intravenous drip.

The utility of the Agent in the treatment of vascular diseases and related conditions in which neutrophil participation is involved or implicated, may be demonstrated in conventional therapeutic intervention trials, in which improvement in clinical or biochemical parameters may be measured. Thus, utility in the treatment of impaired cardiovascular function, for example, myocardial ischaemia, may be assessed by monitoring over a period of at least 2 weeks mortality, morbidity, cardiovascular haemodynamics (such as cardiac output and ejection fraction) and indices of the extent of myocardial damage such as the total release of creatine kinase and LDH.

Similarly, utility in the treatment of impaired cerebrovascular function, for example in treating stroke, may be assessed by monitoring anatomical effects (such as the quantity of damage as assessed by CAT, NMR or other scans) or functional benefit.

Further, utility in the treatment of impaired peripheral vascular function, for example in treating critical limb ischaemia or intermittent claudication, may be assessed by monitoring rest pain or ambulatory distance.

In addition to clinical evaluation in man, the beneficial effects of the Agent may be demonstrated in laboratory animals in experimental paradigms well known in the art.

One such model of coronary arterial thrombosis is, for example, a dog in vivo reperfusion model involving electrically-induced coronary arterial thrombosis and subsequent thrombolysis by administration t-PA, according to the general method described by J L Mehta et al. (Thrombosis Research, 1990, 88, 13-21). The effect of the test substance is assessed by study of any of a variety of

conventional parameters for assessing degree of myocardial ischaemia, for example by study of haemostatic parameters and histological study of the excised myocardium. In particular, the extent of leukocyte accumulation in the myocardium was determined in the ischaemic LAD and non-ischaemic circumflex (Cx) regions in a semiquantitative fashion using the method described by J L Mehta et al. (Am. J. Physiol. 1990, 258, H1402-H1408). This involves grading both the intensity and extent of leukocyte accumulation on a scale of zero to 4 with zero signifying essentially no leukocytes and scale 4 signifying extensive presence in the lumina of microvasculature and the vessel walls, adventitia and myocardial interstitium. By way of example, in this test model, the Agent defined hereinabove when administered as its sodium salt in phosphate buffered saline at the rate of 5mg/kg/hour typically results in a significantly lower amount of leukocyte accumulation without any toxic or other untoward effects being evident during the experiment or from the histological examination.

Another suitable model for evaluation of the Agent in coronary arterial thrombosis is, for example, the conscious dog in vivo model involving electrically-induced coronary arterial thrombosis and infarction according to the general method described by B R Lucchesi et al., (Thrombosis Research, 1980, 17, 841-853) or the modification described by D J Fitzgerald et al. (J. Clin. Invest., 1986, 77, 496-502).

Still further suitable models for evaluation of the Agent in arterial thrombosis are described in the articles by B R Ito et al. (Blood Cells, 1990, 16, 145-166) and B R Lucchesi and K M Mullane (Ann. Rev. Pharmacol. Toxicol., 1986, 26, 201-224).

A suitable model for evaluation of the Agent in cerebrovascular occlusion is, for example, that described in European patent application, publication no. 427,925 involving surgically induced middle cerebral arterial occlusion in rats.

In addition to the above mentioned uses in treating localised vascular disease, the Agent may also be useful in treating or ameliorating those conditions which involve the systemic distribution/accumulation of activated neutrophils, for example in the prevention or reduction of pulmonary leucoembolism, or in treating

haemorrhagic or traumatic shock, and such uses and applications of the Agent therein are included within the ambit of the invention.

The following non-limiting Example illustrates a typical formulation of the Agent for use in the invention.

Example

This example describes a formulation for 4-(4-chlorophenylsulphonylcarbamoyl)benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide (referred to as COMPOUND) which provides a strength of 10 mg/mL as the sodium salt in phosphate-buffered saline and which is suitable for an injectable solution. A corresponding placebo formulation is also provided. The prepared solutions are preferably sealed in ampoules of a convenient size, for example 5 mL, and stored with refrigeration until use.

Ingredient	Weight per mL	
	10.0 mg	Placebo
COMPOUND (Note 1)	10.0 mg	--
Dibasic sodium phosphate, heptahydrate, USP	11.97 mg	10.74 mg
Monobasic sodium phosphate, monohydrate, USP	0.74 mg	1.25 mg
Sodium chloride, USP	4.50 mg	5.48 mg
1 N Sodium hydroxide solution or 0.05 M monobasic sodium phosphate solution (Note 2)	q.s.	q.s.
Water for Injection, USP q.s. ad	1.0 mL (1.01 g)	1.0 mL (1.01 g)

NOTES: (1) The nominal concentration of COMPOUND in this formulation is 10 mg/mL. A manufacturing adjustment is made for the drug substance purity.

(2) Added to adjust pH to 7.0-7.5

Manufacturing directions for the formulation of COMPOUND

1. Charge approximately 90% of the required amount of "Water for Injection, USP" to a vessel equipped with a suitable agitation device, and connected to a heater/cooler circulation bath.

2. Adjust the temperature of the circulation bath to 30 °C.

3. Charge with continuous stirring, the required amount of dibasic sodium phosphate, heptahydrate, USP and continue stirring until dissolved.

4. Charge very slowly with continuous stirring the required amount of COMPOUND.

5. Continue to stir for approximately 30 minutes until dissolved, then decrease the temperature of the circulation bath to 25 °C.

6. Charge with continuous stirring the required amount of monobasic sodium phosphate, monohydrate, USP and continue stirring until dissolved.

7. Charge with continuous stirring the required amount of sodium chloride, USP and continue stirring until dissolved.

8. Measure the pH and adjust to 7.0 to 7.5 with 1 N sodium hydroxide solution or 0.05 M monobasic sodium phosphate solution, if necessary.

9. Bring the batch to final weight (calculated from specific gravity of 1.01) with "Water for Injection, USP".

10. Aseptically filter the bulk solution into a suitable, sterilised filling vessel. Aseptically fill and seal the ampoules.

11. Leak test ampoules and visually inspect for particulate matter and other defects.

Manufacturing directions for the placebo formulation

The procedure listed above is carried out with the omission of steps 2, 4 and 5, and without the need for temperature control.

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What is claimed is:

1. A therapeutic agent for use in the therapeutic or prophylactic treatment of a vascular disease or related condition in which neutrophils are involved or implicated in a mammal, especially a human, in need thereof which agent comprises 4-(4-chlorophenylsulphonylcarbamoyl)benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide, or a pharmaceutically acceptable salt thereof.

2. A therapeutic agent as claimed in Claim 1 wherein the vascular disease or condition to be treated is acute myocardial ischaemia.

3. A therapeutic agent as claimed in Claim 1 wherein the vascular disease or condition to be treated is coronary artery disease or a related disease.

4. A therapeutic agent as claimed in Claim 3 wherein the vascular disease or condition to be treated is myocardial ischaemia or angina.

5. The use of 4-(4-chlorophenylsulphonylcarbamoyl)benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the therapeutic or prophylactic treatment of a vascular disease or related condition in which neutrophils are involved or implicated.

6. The use as claimed in Claim 5 wherein the medicament is for the treatment of acute myocardial ischaemia.

7. The use as claimed in Claim 5 wherein the medicament is for the treatment of coronary artery disease or a related disease.

8. The use as claimed in Claim 5 wherein the medicament is for the treatment of myocardial ischaemia or angina.

9. 4-(4-Chlorophenylsulphonylcarbamoyl)benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide, or a pharmaceutically acceptable salt thereof, for use in treating a vascular disease or related condition in which neutrophils are involved or implicated.

INTERNATIONAL SEARCH REPORT

International application No. PCT/GB 92/01087

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K37/02; A61K37/64

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K ; C07K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	FASEB JOURNAL vol. 2, no. 4, 15 March 1988, BETHESDA, MD US page A346 KRELL R.D. ET AL 'Biochemical characterization of ICI 200880: a novel potent and selective inhibitor of human neutrophil elastase' see abstract 290	1-5,9
X,P	AMERICAN HEART JOURNAL vol. 122, no. 5, November 1991, ST. LOUIS, USA pages 1245 - 1251 NICOLINI F.A. ET AL 'Leukocyte elastase inhibition and t-PA-induced coronary artery thrombolysis in dogs: beneficial effects on myocardial histology' see the whole document	1-9

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° Special categories of cited documents :[10]

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28 SEPTEMBER 1992	
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	FERNANDEZ Y BRA F.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X,P	EP,A,0 458 536 (IMPERIAL CHEMICAL INDUSTRIES PLC) 27 November 1991 see the whole document ---	1-5,9
X,P	EP,A,0 458 537 (IMPERIAL CHEMICAL INDUSTRIES) 27 November 1991 see the whole document ---	1-4,9
X,P	EP,A,0 463 811 (IMPERIAL CHEMICAL INDUSTRIES PLC) 2 January 1992 see the whole document ---	1-4,9
X,P	EP,A,0 458 535 (IMPERIAL CHEMICAL INDUSTRIES PLC) 27 November 1991 see the whole document ---	1-4,9
X	EP,A,0 189 305 (ICI AMERICAS INC.) 30 July 1986 cited in the application see the whole document -----	1-4,9

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201087 SA 61589

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0458536	27-11-91	AU-A- 7719591	28-11-91
EP-A-0458537	27-11-91	AU-A- 7719491	28-11-91
EP-A-0463811	02-01-92	AU-A- 7924191	02-01-92
		US-A- 5128322	07-07-92
EP-A-0458535	27-11-91	AU-A- 7719791	28-11-91
EP-A-0189305	30-07-86	AU-B- 594658	15-03-90
		AU-A- 5262386	31-07-86
		JP-A- 61218518	29-09-86
		US-A- 4910190	20-03-90
		US-A- 5055450	08-10-91